Remarks

Claims 45-56 are pending in the application.

I. Objections

The Examiner has objected to claim 51 for a typographical error. (Office Action, page 2.) Applicants thank the Examiner for pointing out this error and have amended claim 51 to correct the error.

II. Rejection of the Claims Under 35 U.S.C. § 112, second paragraph

Claim 47 stands rejected under 35 U.S.C. § 112, second paragraph as being indefinite. (Office Action, page 2.) The Examiner asserts that it is unclear which of the nucleic acid molecules of molecules of step (b) are referenced by the claim. Applicants have amended claim 47 to recite "the nucleic acid molecule produced in step (b)" to clarify this point. The Examiner has further noted claim 47 when read in its entirety does not make sense. Applicants don not agree but in order to advance prosecution have amended claim 47 to recite "thereby preventing homologous recombination between the nucleic acid molecule produced in step (b), the at least three additional nucleic acid molecules, and the first and second nucleic acid molecules" to make it clear that the lack of sufficient homology for homologous recombination prevents homologous recombination.

Claims 45-56 stand rejected under 35 U.S.C. § 112, second paragraph as being incomplete for omitting essential steps. (Office Action, page 3.) The Examiner asserts that the invention does not clearly set forth how the preamble of the claimed invention produces a replication-incompetent virus. Applicants have amended step (c) of claim 45 to recite "a cell that packages the nucleic acid molecule generated in step (b) such that the packaging signal of the first nucleic acid molecule is present *in trans.*" As discussed in paragraph [0037] and elsewhere in the specification, when requisite packaging activities such as a packaging signal are provided *in trans*, a replication-defective virus results. Applicants believe that amended claim 45 provides all of the steps necessary to produce a replication-incompetent virus as recited in the preamble and therefore the claim is fully compliant with 35 U.S.C. § 112, second paragraph.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

III. Rejection of the Claims Under 35 U.S.C. § 103(a)

Claims 45-48, 50 and 52-56 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over von Melchner *et al.* (*Blut, 57*:1-5, 1988) and Hartley *et al.* (*Genome Res., 10*:1788-1795, 2000). (Office Action, page 4.) Applicants respectfully disagree.

The Examiner asserts that von Melchner *et al.* describe recombinant retroviruses containing a foreign gene which may be used for gene transfer into hemopoietic cells and that Hartley *et al.* discloses DNA cloning using site-specific recombination which may be used for protein expression. (Office Action, page 4.) However, the cited art fails to disclose all of the limitations of the claims and the Examiner has failed to provide sufficient rationale for why one skilled in the art would combine the to arrive at the claimed invention.

Vectors used in methods of the claimed invention include safety features intended to lessen the probability of a vector component becoming incorporated into a replication competent retrovirus. These Safety features include:

1) Lack of sufficient retroviral components to form a retroviral replication complex.
2) Use of multiple vectors which encode different components for forming retroviral particles.
3) Lack of sufficient homology to undergo homologous recombination with each other or the first and second nucleic acid molecules. This reduces the likelihood of homologous recombination between the vectors or with retroviruses which may be resident in cells (see dependent claim 47).
4) Lack of long terminal repeats in vectors not intended for incorporation into retroviral particles.

As amended herein, claim 45 is directed, in part, to a method of constructing a recombinant retrovirus wherein a first nucleic acid molecule lacks "retroviral sequences which produce retroviral gene products and which comprises a 5'-long terminal repeat, a 3'-long terminal repeat, a packaging signal" and "introducing the nucleic acid molecule generated in step (b), with at least three additional nucleic acid molecules which encode retroviral proteins, into a cell that packages the nucleic acid molecule generated in step (b) such that the packaging signal

of the first nucleic acid molecule is present *in trans*." Claim 46 further recites that elements necessary for proper packaging of a retrovirus are missing from the at least three additional nucleic acid molecules while claim 47 further recites that "the nucleic acid molecule of step (b), the at least three additional nucleic acid molecules lack sufficient homology to undergo homologous recombination with each other or the first and second nucleic acid molecules."

As noted by the Examiner, von Melchner *et al.* does not discuss lack of sufficient homology to prevent homologous recombination and does not discuss the use of three additional nucleic acids. Figure 1 of von Melchner *et al.* only depicts a total of two nucleic acid molecules, not the four molecules of the presently claimed invention. The Examiner appears to rely on Hartley *et al.* for the use of multiple nucleic acid molecules when she states "[T]he author describes the in vitro site-specific recombination method as a method allowing numerous DNA segments to be transferred in parallel in may vector backgrounds." (Office Action, page 5.) However, Hartley *et al.* is discussing the multiple molecules in the context of site-specific recombination which is used in step (b) of claim 45 but which is unrelated to the at least three additional molecules recited in step (c) of claim 45.

Neither von Melchner *et al.* nor Hartley *et al.* discuss homologous recombination. In the claimed method, genes encoding components required for packaging are separated into multiple nucleic acid molecules which lack sufficient homology to undergo homologous recombination, helping to lessen the possibility of generating a replication-competent retrovirus. The Examiner asserts that "it would have been obvious for the ordinary artisan to prevent separate DNA molecules from undesired homologous recombination for optimization of results" but provides no rational for this assertion. Further the Examiner has not provided a rational for why one skied on the art would combine all four of the safety features discussed above and present in the claims. Without these rationale, a *prima facie* case of obviousness has not been established.

Applicants assert that neither von Melchner e*t al.* or Hartley *et al.*, alone or in combination, teach or suggest the presently claimed method.

Claims 45, 46 and 49-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over von Melchner *et al.* in view of Hartley *et al.*, Ping *et al.* (*RNA, 3*:850-860, 1997) and Hopkins (*PNAS., 90*:8759-8760, 1993). (Office Action, page 6.) Applicants respectfully disagree.

As discussed above, Applicants do not believe that a prima facie case of obviousness has been established for independent claim 45. Neither Ping *et al.* or Hopkins remedy the deficiencies in von Melchner *et al.* and Hartley *et al.* discussed above therefore a *prima facie* case of obviousness has not been established.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a).

Conclusion

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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